Attachment II

Attachment II – Description of New Literature Search (Preclinical and Clinical)

Analysis of Original Bibliography

As part of the effort to review and update the literature search to address comments received from the agency, RS Medical first revisited the 165 articles from the original bibliography. The two articles pertinent to clinical studies that were missed during the initial analysis were initially discussed in Attachment I and were then further analyzed in Attachment III.

Among the original 165 articles from the original search, there were already references pertaining to preclinical investigation (16), including cell culture, animal studies and investigations into the mechanism of action, and additional general information (9) related to treatment with electrical stimulation. These articles were also obtained for further review; however, in-depth analyses will not be presented for all of these articles or categories. The point remains that, with the original search parameters, information regarding these aspects of the use of electrical stimulation was obtained.

Additional Searches

New searches of the Pubmed database were focused on obtaining additional information related to preclinical work or animal models and additional published clinical trials. The only limitation imposed on these searches was a restriction to English language articles only. Initially, the key-word list was lengthy and detailed, with combinations of the general key-words from the original search and additional more specific key-words listed below (Table 1).

Table 1. Keywords

General Keywords	Additional Specific Keywords
Pulsed electromagnetic fields	Osteogenic tissues
Capacitively coupled	Osteogenesis
Capacitively coupled electric field	Experimental
Electromagnetics	Healing
Electromagnetic fields	Osteoblast
Clinical trials	Osteogenic tissue
Fracture healing	Costochondral junctions
Bone growth	Cartilage
Preclinical	Mechanical testing
Cell culture	Stimulation
Animal models	Ossification
Clinical	Effectiveness
Nonunions	Safety
Bone growth	
Nonunions	
Electrical stimulation	

Use of these more specific key-words did not result in an expansion of the citation base, but was actually more limiting. Thus, the combinations and resulting citations shown in Table 2 were pursued.

Table 2. Literature Searches for Preclinical and Clinical Effects of Electrical Stimulation

Keyword Combinations	Number of Citations
Pulsed electromagnetic fields OR capacitively coupled OR capacitive coupling	861 (30 titles selected for abstract review)
Pulsed electromagnetic fields OR capacitively coupled OR capacitive coupling AND bone stimulation	1
Pulsed electromagnetic fields OR capacitively coupled OR capacitive coupling AND bone stimulator	1
Pulsed electromagnetic fields OR capacitively coupled OR capacitive coupling AND clinical trials	70
Capacitively coupled OR capacitive coupling OR pulsed electromagnetic fields OR electrical stimulation AND nonunions	56
Pulsed electromagnetic fields OR capacitively coupled OR capacitive coupling AND animals	41
Pulsed electromagnetic fields AND animal model AND preclinical AND animals OR cells AND experimental AND electromagnetics AND electrical stimulation OR capacitively coupled electric field AND electromagnetic fields	23
Pulsed electromagnetic fields AND animal models AND bone growth OR repair OR Capacitively coupled electric field	17
Pulsed electromagnetic fields AND animal models	15
Pulsed electromagnetic fields AND animal models AND bone growth repair OR capacitively coupled electric field	38
Pulsed electromagnetic fields OR capacitively coupled OR electromagnetics OR electromagnetic fields AND animal models AND fracture healing	5
Pulsed electromagnetic fields OR capacitively coupled OR electromagnetics OR electromagnetic fields AND animal model OR cell culture AND bone growth	350 (chose 6 and looked at 1,969 related article titles)
Pulsed electromagnetic fields OR capacitively coupled OR electromagnetics OR electromagnetic fields AND animal models AND bone growth	8
Pulsed electromagnetic fields OR capacitively coupled OR electromagnetics AND clinical trials AND bone growth	9
Pulsed electromagnetic fields OR capacitively coupled OR electromagnetics OR electromagnetic fields AND clinical trials AND fracture healing AND bone growth	3
Capacitive coupl* OR capacitively coupled OR pulsed electromagnetic fields AND nonunions	21

During this search and review process, all 1,519 article titles originally identified by this new search combination (total of primary numbers in Table 2) were reviewed for pertinence. Six articles were identified as potentially pertinent from the combination yielding 350 citations. But these six articles yielded another 1,969 related articles, all of which received title reviews. Thus, a total of 3,488 titles were reviewed for relevance. There was overlap among these searches, with some citations appearing repeatedly among the keyword parameters. Among these new searches, articles from the search conducted for the original reclassification petition (165 articles) were located. The final 41 articles reviewed in the original petition were also located, along with the 2 additional pertinent which are discussed in Attachments II and III of this document.

Subsequent to the title review described above and eliminating titles which had already been considered through the original search, abstracts of 180 selected titles were reviewed. Fifty-nine additional articles (59) were obtained for in-depth analysis: 35 new articles and 24 which already existed from the original search of 165 (see Table 3).

Table 3. Relevant Preclinical and Clinical Articles

Type of Citation	Number	In Original Bibliography
Preclinical – Cell Culture Models	20	4
Preclinical – Animal Models	24	15
Clinical Work	15	5

Pertinent information from these additional articles (40) relevant to this reclassification petition is discussed in Attachment III. A bibliography also appears in Attachment IX.